Regulation of the Aurora-A gene following topoisomerase I inhibition: implication of the Myc transcription factor.

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Résumé en anglais	During the G2 phase of the cell cycle, the Aurora-A kinase plays an important role in centrosome maturation and progression to mitosis. In this study, we show in colorectal cell lines that Aurora-A expression is downregulated in response to topoisomerase I inhibition. Using chromatin immunoprecipitation assays, we have observed that the Myc transcription factor and its Max binding partner are associated with the Aurora-A promoter during the G2 phase of the cell cycle. RNA interference experiments indicated that Myc is involved in the regulation of the Aurora-A gene. Following topoisomerase I inhibition, the expression of Myc decreased whereas Mad was upregulated, and the association of Myc and Max with the promoter of the kinase was inhibited. In parallel, an increased association of Mad and Miz-1 was detected on DNA, associated with an inhibition of the recruitment of transcriptional coactivators. Interestingly, a gain of H3K9 trimethylation and HP1gamma recruitment was observed on the Aurora-A promoter following sn38 treatment, suggesting that this promoter is located within SAHF foci following genotoxic treatment. Since Aurora-A is involved in centrosome maturation, we observed as expected that topoisomerase I inhibition prevented centrosome separation but did not affect their duplication. As a consequence, this led to G2 arrest and senescence induction.These results suggest a model by which the Aurora-A gene is inactivated by the G2 checkpoint following topoisomerase I inhibition. We therefore propose the hypothesis that the coordinated overexpression of Myc and Aurora-A, together with a downregulation of Mad and Miz-1 should be tested as a prognosis signature of poor responses to topoisomerase I inhibitors.

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